Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study

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Background and purpose: Age related white matter changes (ARWMC) are frequent in non-demented old subjects and are associated with impaired cognitive function. Our aim was to study the influence of vascular risk factors and ARWMC on the neuropsychological performance of an independent elderly population, to see if vascular risk factors impair cognition in addition to the effects of ARWMC.

Methods: Independent subjects, aged 65–84 years, with any degree of ARWMC were assessed using a comprehensive neuropsychological battery including the Mini-Mental State Examination (MMSE), VADAS-Cog (Alzheimer's disease assessment scale) and the Stroop and Trail Making test. Vascular risk factors were recorded and ARWMC (measured by MRI) were graded into three classes. The impact of vascular risk factors and ARWMC on neuropsychological performance was assessed by linear regression analyses, with adjustment for age and education.

Results: 638 patients (74.1 (5) years old, 55% women) were included. Patients with severe ARWMC performed significantly worse on global tests of cognition, executive functions, speed and motor control, attention, naming and visuoconstructional praxis. Diabetes interfered with tests of executive function, attention, speed and motor control, memory and naming. Arterial hypertension and stroke influenced executive functions and attention. The effect of these vascular risk factors was independent of the severity of ARWMC, age and education.

Conclusion: ARWMC is related to worse performance in executive function, attention and speed. Diabetes, hypertension and previous stroke influenced neuropsychological performance, independently of the severity of ARWMC, stressing the need to control vascular risk factors in order to prevent cognitive decline in the elderly.

Cerebral age related white matter changes (ARWMC) are frequently described on brain imaging in demented and non-demented elderly subjects.[1 2] Some demographic and vascular risk factors are associated with a higher risk of developing ARWMC, with major emphasis on age, hypertension and stroke.[3–6] On the other hand, recent epidemiological evidence indicates that vascular risk factors play a role in the development of cognitive impairment and dementia, including degenerative dementia.[7–11] ARWMC can be a mediator between vascular risk factors and cognitive decline, while some demographic characteristics can contribute towards protecting cognitive function.[12] Our aim was to study the influence of ARWMC and vascular risk factors on the neuropsychological performance of non-disabled independent elderly people with ARWMC and to analyse if vascular risk factors had an independent effect on cognitive performance.

METHODS

The LADIS (Leukoaraiosis and Disability) study is a prospective multinational European project investigating the independent impact of ARWMC on the transition to disability in the elderly. The rationale, methodology and baseline assessment have been described previously.[12 13] Investigators were provided with a specifically developed handbook with guidelines for applying criteria and tools.[13] In short, inclusion criteria for the study were: (i) 65–84 years of age; (ii) changes in ARWMC on MRI of any degree, according to the scale of Fazekas and colleagues[14]; and (iii) no disability, as determined by the Instrumental Activities of Daily Living scale.[15] Patients were enrolled because of minor neurological, cognitive or motor complaints, or incidental findings on cranial imaging caused by non-specific events, as detailed elsewhere.[13] To assess vascular risk factors, trained medical personnel used a structured and comprehensive questionnaire together with review of the available records. A detailed description of the study variables has been reported previously.[13] Those germane to this study are the vascular risk factors.[6] Vascular risk factor criteria have been described in detail previously.[6] Detailed criteria are given in appendix 1 (appendix 1 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). In short, these risk factors were: previous hypertension: current antihypertensive treatment or blood pressure values ⩾140/90 mm Hg in subjects not taking antihypertensive medication, based on multiple blood pressure measurements on several separate occasions; diabetes mellitus: previous diagnosis and/or current treatment with insulin or oral hypoglycaemic medications, or an 8 h fasting plasma glucose level of ⩾7.0 mmol/l or 126 mg/dl; hyperlipidaemias: total cholesterol >200 mg/dl, low density

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; ARWMC, age related white matter changes; LADIS study, Leukoaraiosis and Disability study; MMSE, Mini-Mental State Examination; TM, Trail Making

lipoprotein >130 mg/dl, high density lipoprotein <35 mg/dl and triglyceride >200 mg/dl, on at least two occasions; myocardial infarction; angina pectoris; heart failure; atrial fibrillation; lower limb arteriopathy and peripheral vascular disease; history of stroke and/or transient ischaemic attack; cigarette smoking, expressed as smoked pack-years; alcohol consumption, expressed as g/day consumed, with one drink containing 10 g of alcohol. Subjects were classified as past drinkers, not drinkers (never drinkers) and current drinkers (subdivided into sporadic drinkers (<1 drink/week), low drinkers (≥1 drink/week but <1 drink/day), moderate drinkers (1–3 drinks/day) and heavy drinkers (>4 drinks/day)).

The degree of ARWMC severity was rated on FLAIR sequences by central readers blind to the clinical data using the three severity classes in the revised version of the visual scale of Fazekas and colleagues.[14] Medial temporal lobe atrophy was assessed on coronal T1 weighted sequences using the MTA scale.[16]

Neuropsychological assessment

The LADIS neuropsychological battery has been described in detail elsewhere.[12] The neuropsychological battery included the Mini-Mental State Examination (MMSE)[17] as a global measure of cognitive function; the VADAS-Cog (Alzheimer's Disease Assessment Scale (ADAS-Cog) plus delayed recall, symbol digit, digit span, mazes, digit cancellation and verbal fluency) as a comprehensive instrument to assess orientation, language, ideational and constructional praxis, immediate memory and delayed recall)[18]; and the Stroop[19 20] and Trail Making (TM) test[21] as measures of executive function. Tests were grouped by cognitive domains, as follows: executive functions (Stroop, verbal fluency and TM); attention (digit cancellation and symbol digit test); speed and motor control (Trail A and time to complete maze test); memory (digit span, word recognition, word recall, delayed recall); language (commands and naming); praxis (visuoconstructional and ideational praxis; ADAS subtests). To analyse performance by domain, a compound measure for three main domains was calculated using standard scores for individual tests, as described previously[12]: (1) memory = z scores of (immediate word recall + delayed recall + word recognition + digit span)/4; (2) executive functions = z scores of ((Stroop3-2) + (TMB-TMA) + symbol digit + verbal fluency)/4; and (3) speed and motor control = z scores of (TMA + mazes + digit cancellation)/3. Z scores of the tests that had higher scores representing worse performance were inverted (−Z) in order to calculate the compound measure score.

Statistical analysis

Scores of neuropsychological tests were considered as continuous variables. The influence of vascular risk factors and severity of ARWMC (three grades) on neuropsychological performance was analysed by t tests for variables with two levels and one way ANOVAs for variables with more than two levels. Adjustment of α for multiple comparisons was performed with Bonferoni statistics. Alcohol intake effect was analysed by dividing current by past and never drinkers. The effect of the quantity of alcohol on neuropsychological performance was analysed using one way ANOVA.

Linear regression analyses were performed to evaluate the impact of vascular risk factors and ARWMC on scores for the different cognitive domains and individual neuropsychological tests. In the first model, we included vascular risk factors as independent variables. In the second model, we added ARWMC to determine if the effect of vascular risk factors in neuropsychological tests was independent of the effect of ARWMC. Linear regression analyses were adjusted for age, education,[12] lacunes,[22] medial temporal lobe atrophy and visual deficit. The independent variables included in linear regression analyses were selected from the bivariate analysis, with $p<0.1$ as the screening criterion for selection of the variables. Infrequent vascular risk factors (less than 5% frequency in the study population) were excluded from linear regression analyses.

Data were analysed using SPSS 12.0 software.

RESULTS

From the 639 patients in the LADIS cohort, one patient was excluded because of incomplete neuropsychological evaluation and hence 638 patients were included in the present study. Table 1 shows the patient characteristics and risk factors relevant to the present study.

Influence of ARWMC severity on neuropsychological evaluation

Analyses of variance (ANOVA) showed significant differences in performance on the neuropsychological tests according to the severity of ARWMC, most notably when comparing mild with severe ARWMC (table 2). Patients with severe ARWMC performed significantly worse on: (a) global measures of cognition (MMSE and ADAS total score), (b) compound measures of executive functions, speed and memory, (c) all individual tests of the same domains, (d) attention and (e) individual tests of memory, language and visuoconstructional praxis.

Influence of vascular risk factors on neuropsychological evaluation

T test results (data given in appendix 2; appendix 2 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental) showed that patients with hypertension performed significantly worse ($p \leqslant 0.001$) on the compound measure of executive functions, and on Stroop, TM and symbol–digit tests. Patients with diabetes had worse performance ($p \leqslant 0.001$) on TM, symbol–digit test and immediate word recall tests. Patients with previous stroke had worse performance ($p \leqslant 0.001$) on the digit cancellation, symbol digit tests and on the compound measure of executive functions.

Table 1 Baseline patient characteristics (n = 638)

Age (y) (mean (SD))	74.1 (5)
Sex (F/M)	351 (55%)/287(45%)
Educational level (years of schooling)	9.6 (3.8)
Vascular risk factors (frequency)	
Hypertension	445 (69.6%)
Diabetes mellitus	92 (14.4%)
Previous stroke	188 (29.4%)
Previous transient ischaemic attack	115 (18%)
Atrial fibrillation	49 (7.7%)
Angina pectoris	98 (15.3%)
Heart failure	21 (3.3%)
Myocardial infarction	72 (11.3%)
Cardiac valvulopathy	27 (4.2%)
Cardiac arrhythmias (other than atrial fibrillation)	75 (11.7%)
Peripheral vascular disease	45 (7%)
Hypercholesterolaemia	315 (49.3%)
Hypertriglyceridaemia	96 (15%)
Alcohol consumption (current)	309 (48.4%)
Alcohol consumption (past)	41 (6.4%)
Smoking (current)	68 (10.7%)
Smoking (past)	224 (35.1%)
ARWMC	
Mild	284 (44.5%)
Moderate	196 (30.7%)
Severe	158 (24.8%)

ARWMC, age related white matter changes.

Table 2 Mean raw scores of neuropsychological tests according to ARWMC severity, and ANOVA comparing performance on the neuropsychological tests in terms of severity of ARWMC

	Executive functions					Attention		Speed/motor control		Memory				Language		Praxis		
ARWMC severity	MMSE	Stroop 3–2	Verbal fluency	Trail B-A	Executive functions (compound measure)	Digit cancellation	Symbol digit	Trail A	Maze	Speed (compound measure)	Digit span	Word recognition	Immediate word recall	Delayed word recall	Memory (compound measure)	Commands	Naming	Visuo-constructional praxis	Ideational praxis	ADAS (total score)
Mild	27.7	30.1	20.2	95.3	0.71	21.5	29.7	56.6	6.7	0.4	5.6	2.7	5.1	5.5	0.25	0.35	0.14	0.45	0.12	15.4
Moderate	27.4	33.7	19.1	108.7	0.04	19.0	26.0	64.3	7.3	0.02	5.5	2.9	5	6.1	−0.04	0.33	0.18	0.72	0.29	17.2
Severe	26.7	42.6	16.6	125.7	−0.81	16.6	22.4	75.2	8.9	−0.58	5.1	3	5.3	6.1	−0.38	0.41	0.27	0.65	0.22	18.2
F	9.6**	10.5**	16.5**	11.8**	19.6**	28.8**	24.2**	12.9**	6.4**	13.7**	4.1*			5.8**	3.8*		4.2*	9.6**	4.6*	8.8**
Difference between groups†	bc	bc	bc	bc	abc	abc	abc	bc	bc	bc	c			ac	c		c	ac	A	ac

ADAS, Alzheimer's Disease Assessment Scale; ARWMC, age related white matter changes; MMSE, Mini-Mental State Examination.
Only statistical significant results are showed: *p<0.01; **p<0.001.
†Differences between groups: (a) significant difference between mild and moderate ARWMC; (b) significant difference between moderate and severe ARWMC; (c) significant difference between mild and severe ARWMC.

Current alcohol intake was associated with better performance ($p \leqslant 0.001$) on MMSE comparing past with never drinkers.

Linear regression analyses

Results of linear regression analyses to evaluate the impact of ARWMC and vascular risk factors on neuropsychological performance are shown in table 3. Results concerning global measures of cognition and compound measures are also shown in table 3. Results of regression analyses with individual tests can be found in appendix 3 (appendix 3 can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental) (positive results are described in the text). Linear regression analyses were repeated excluding stroke patients (188 patients), and controlling for atrophy, lacunes[22] and visual deficit (as potential confounders on the performance of neuropsychological tests) and produced similar results (data available on request).

Diabetes influenced the performance on the global measure of cognition (ADAS total score), compound measures of executive functions, speed and memory. Diabetes also influenced tests of attention, language, praxis and some tests of memory (word recall and delayed word recall). Arterial hypertension was associated with worse performance on the compound measure of executive functions, Trail B-A and symbol digit tests. Stroke was associated with lower performance on the compound measure of executive functions, on Stroop test 3–2, and tests of attention (digit cancellation) and memory (immediate word recognition). Patients with peripheral vascular disease performed significantly worse on global measures (MMSE and ADAS total score), on the compound measure of memory and on word recall test. Patients with current alcohol intake had better performance on the MMSE, on mazes, word recall and commands tests and on the compound measure of speed, comparing never and past drinkers. Patients with current alcohol intake were not otherwise different on global status or other associated risk factors. Using one way ANOVA to evaluate the impact of alcohol quantity intake on neuropsychological performance, moderate (1–3 drinks/day) and low drinkers ($\geqslant$1 drink/week but $<$1 drink/day) performed significantly better on the MMSE than never drinkers (27.95 vs 26.99 ($p<0.05$) and 27.88 vs 26.99 ($p<0.01$)). No differences were found for severe drinkers. Introducing ARWMC into the model, we found that it was independently related to worse performance on global measures of cognition (MMSE and ADAS total score), compound measures of executive functions and speed/motor control in all tests of executive functions, attention, language (naming) and visuoconstructional praxis. Education interfered with all neuropsychological tests and the effect of age was retained.[12] The presence of visual deficits and lacunes did not change the impact of vascular risk factors on neuropsychological performance.

DISCUSSION

This study confirmed that the severity of ARWMC is related to worse performance on global measures of cognition, executive functions, speed/motor control and tests of attention, naming and visuoconstructional praxis. In previous studies, ARWMC were associated with cognitive deficits in independent elderly subjects, mainly in executive functions, attention, speed and motor control[23 24] but also with global measures of cognition,[1 4 23 25] visuoconstructional[1 23] and memory tasks.[3] However, the association was not consistent across all studies. We had the opportunity to study the impact of ARWMC and simultaneously the impact of clinical vascular risk factors on neuropsychological performance, controlling for demographic variables and atrophy. We found that even controlling for the

Table 3 Impact of vascular risk factors on neuropsychological performance: cognitive domains (linear regression analysis; global tests MMSE and ADAS total and compound measures; executive functions; speed and motor control; and memory)

Cognitive measure	Independent variables	R square	R square change	F change	β standard
MMSE					
Model 1		0.16	0.16	17.16**	
Model 2	Age	0.17	0.01	9.4**	NS
	Education				0.32**
	Hypertension				NS
	Diabetes				NS
	PVD				−0.08*
	Cardiac arrhythmias				NS
	Current alcohol				0.13**
	ARWMC				−0.12**
ADAS total score					
Model 1		0.14	0.14	20.59**	
Model 2	Age	0.16	0.01	9.12**	0.15**
	Education				−0.27**
	Hypertension				NS
	Diabetes				0.13**
	PVD				0.11**
	ARWMC				0.12**
Executive functions (compound measure)					
Model 1		0.27	0.27	29.46**	
Model 2	Age	0.29	0.02	15.58**	−0.21**
	Education				0.38**
	Hypertension				−0.38*
	Previous stroke				−0.1*
	Diabetes				−0.11**
	PVD				NS
	Angina pectoris				NS
	ARWMC				0.15**
Speed and motor control (compound measure)					
Model 1		0.19	0.19	20.5**	
Model 2	Age	0.21	0.02	15.23**	−0.16**
	Education				0.34**
	Hypertension				NS
	Previous stroke				NS
	Previous TIA				NS
	Diabetes				−0.03**
	Current alcohol				0.01*
	ARWMC				−0.15**
Memory (compound measure)					
Model 1		0.13	0.13	12.57	
Model 2		0.14	0.01	NS	
	Age				−0.15**
	Education				0.27**
	Hypertension				NS
	Diabetes				−0.11**
	PVD				−0.1*
	Hypertriglyceridaemia				NS
	Current alcohol				NS
	ARWMC				NS

ADAS, Alzheimer's Disease Assessment Scale; ARWMC, age related white matter changes; MMSE, Mini-Mental State Examination; PVD, peripheral vascular disease; TIA, transient ischaemic attack.
Results of β standard are presented only for model 2.
*$p<0.05$; **$p<0.01$.

severity of ARWMC and atrophy, vascular risk factors (such as diabetes, hypertension and previous stroke) emerged as relevant variables with an influence on neuropsychological tests. These results suggest that vascular risk factors impair cognition, independent of cerebral damage measurable, using current radiological methods. It is, however, conceivable that other imaging methods (eg, diffusion tensor MRI) might have demonstrated more extensive ARWMC and probably a less independent effect of vascular risk factors.[26]

Our study has some limitations. The sample was selected based on minor complaints, and probably represents the first moment when non-disabled elderly people with cerebral white mater changes seek medical attention. However, this sample does not represent the global community. To increase consistency and homogeneity in the whole assessment, investigators were provided with a specifically developed handbook with guidelines for applying criteria and tolls.[13] The methodology and inclusion criteria were uniform in all centres.[13] Sociocultural and nutritional differences between countries and consequent variation between vascular risk factors profile in the included population may limit the external validity of the results. However, the possible heterogeneity provided by linguistic, cultural and educational differences of the LADIS cohort makes the results more consistent and generalisable, as they are from a large sample with a wide variety of subjects. Moreover, validation and harmonisation of instruments and procedures among centres, including the neuropsychological battery, was done prior to the beginning of inclusion of subjects, as discussed elsewhere.[12] Differences across centres were evaluated and could not explain the results.[12] To exclude

possible interference on the performance of neuropsychological tests, visual deficits were considered in the regression analysis.

Recent evidence found that diabetics have a higher risk of dementia, including Alzheimer's disease,[10 27] and that non-demented diabetic patients performed worse on several cognitive tasks compared with healthy controls.[27 28] However, in these studies, ARWMC was not taken into account. A recent study found that patients with type 2 diabetes had a worse performance on attention, executive functions, processing speed and memory, which was associated with ARWMC.[29] In our study, diabetes was found to be the most important vascular risk factor interfering with global tests, compound measures of executive functions, speed/motor control and tests of attention, memory, praxis and language. This association was independent of the degree of ARWMC, atrophy, age, education and presence of visual deficits.

Cognitive changes and higher risk of dementia have been reported in patients with hypertension,[8 9 30] and recent results of trials using antihypertensive medication suggest a beneficial effect on cognition.[31] Van Swieten and colleagues[30] also found that patients with hypertension with confluent ARWMC performed worse on tests of executive functions (TM and Stroop), MMSE and the Wechsler Memory Scale visual subtest, but not on other memory tests. Sierra *et al* found that middle-aged hypertensive patients with ARWMC performed significantly worse than hypertensive patients without ARWMC on the digit span forward task.[32] We found that hypertension was associated with a worse performance on tests of attention and mental flexibility, but not on other tests. One possible explanation for the relatively modest impact of hypertension may be related to the low proportion of non-hypertensive subjects (only 30%) in the LADIS sample.

In a previous study, ARWMC was related to speed and attention in stroke survivors,[33] and stroke was proposed as a mediator between cerebral small vessel disease and cognitive decline.[34] We found previous stroke to be associated with worse performance on mental flexibility, attention and memory recognition tests, independent of the severity of ARWMC.

The influence of alcohol intake on brain structure and cognition is a controversial issue. Recent studies suggested that light to moderate alcohol consumption is associated with a reduced risk of dementia.[35] Conversely, brain atrophy is associated with alcohol intake, even for low intake drinkers,[36] and controversial effects on ARWMC and infarcts were reported. We found that mild and moderate drinkers performed better on global evaluation (MMSE) than non-drinkers, independent of education, age and ARWMC, but no other association was found between alcohol intake and neuropsychological testing, even when heavy drinkers were included. These results could possibly reflect a ''survival'' bias.

In conclusion, the neuropsychological performance of independent elderly subjects with ARWMC was influenced by biological and demographic variables: severity of ARWMC, some vascular risk factors, but also age and education[12]. These results emphasise the key role of risk factor control for the prevention of dementia and cognitive impairment.

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